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Pharyngotonsillitis

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Acute pharyngotonsillitis is a common illness that often leads patients to consult general practitioners, pediatricians, internists, ear, nose and throat physicians, and other types of primary-care doctors. The disease results in a high degree of absence from daycare, school and work.

The highest incidence of pharyngotonsillitis occurs during the winter season and among individuals in the 5–15 years age-group (28). Pharyngotonsillitis can be caused by a wide variety of pathogens (Table 1). Viruses account for over 50% of all cases of pharyngotonsillitis (2). Of bacterial pathogens, beta-hemolytic group A streptococci (e.g. *Streptococcus pyogenes*) are responsible for 15–30% of all cases of pharyngotonsillitis, with higher rates of occurrence during the winter months in temperate climates (3, 13, 86, 92). Patients with pharyngotonsillitis caused by beta-hemolytic group A streptococci are candidates for antibiotic treatment. However, it is of utmost importance to prevent the over-prescription of antibiotics for pharyngotonsillitis that is not caused by beta-hemolytic group A streptococci, and prescription of antibiotics should especially be avoided for patients in whom the disease is caused by a virus (50). As described below, patients in whom sore throat is caused by bacteria other than beta-hemolytic group A streptococci may also benefit from antibiotic therapy.

Patients with severe symptoms, such as difficulties in swallowing, or dysphonia or stridor, must be evaluated for 'deeper' throat infections, such as epiglottitis, peritonsillitis, parapharyngeal abscess and Lemierre's syndrome. These illnesses, however, are not discussed in this article. This review deals exclusively with pharyngotonsillitis.

Beta-hemolyic group A streptococci

Grouping of streptococci

Identification of bacterial strains constitutes the basic tool in studies of the epidemiology and treatment outcome of pharyngotonsillitis. The streptococcal group of organisms are classified into Lancefield's serological groups A–U according to carbohydrate antigens in the cell wall. Based on the presence of T antigen, beta-hemolytic group A streptococci are divided into about 30 T types (46).

Further subdivision of group A streptococci is made on the basis of the M-protein (45). DNA technologies of the past decade has resulted in the classification of the M-type of beta-hemolytic group A streptococci based upon the sequence of the M-type gene *emm*, and more than 120 *emm*-sequence types have been identified (20).

Virulence factors

Beta-hemolytic group A streptococci possess a multitude of extracellular and cell-bound virulence factors, which aid in various stages of tissue invasion and are responsible for different disease manifestations.

The cell wall M-protein, an extended alpha-helical protein with anticomplementary and antiphagocytic properties, is considered as the main virulence determinant of beta-hemolytic group A streptococci. M-proteins, by interacting with plasma proteins such as immunoglobulin G, fibrinogen and C4-binding protein, are able to interfere with innate and adaptive host immune responses (9). As recognized for decades, only type-specific antibodies directed towards the N-terminal part of the M-protein will be opsonic and protect against beta-hemolytic group A streptococcal disease (24).

The hyaluronic capsule, although poorly expressed *in vitro*, is a second antiphagocytic factor of beta-hemolytic group A streptococci (90). The T-protein, previously not implicated as biologically important, was recently shown to be present in fimbriae-like structures in beta-hemolytic group A streptococci and probably plays a role in tissue adhesion (56). Pyrogenic exotoxins (erythrogenic toxins) are superantigens capable of triggering T lymphocytes to

Table 1. Infectious agents of pharyngotonsillitis

Beta-hemolytic streptococcus group A
Beta-hemolytic streptococcus group C and group G
Arcanobacterium hemolyticum
Corynebacterium diphtheriae
Spirochetes and fusiform bacteria (Vincent's angina)
Neisseria gonorrhoeae
Mycoplasma pneumoniae
Chlamydia pneumoniae
Adenovirus
Epstein–Barr virus
Cytomegalovirus
Rhinovirus
Parainfluenza virus
Respiratory syncytial virus
Coronavirus
Herpes simplex virus
Coxsackie A virus
Influenza A and B viruses
Human immunodeficiency virus (primary infection)

release massive amounts of cytokines and interleukins, thereby generating severe symptoms such as fever, the scarlatiniform rash, tissue necrosis, hypotension and organ failure (4). The cysteine protease (identical to exotoxin SpeB) according to experimental work may be essential for circulatory shock and lung damage (31, 32). This enzyme, and a second cysteine protease of beta-hemolytic group A streptococci, may cleave immunoglobulin G, thereby interfering with immune opsonization of beta-hemolytic group A streptococci. Streptolysins S and O are capable of lysing erythrocytes as well as leukocytes and platelets (26, 77). Streptokinase, which converts plasminogen to plasmin, may significantly contribute to a rapid spread of beta-hemolytic group A streptococci within infected tissue by lysing blood clots (51).

Internalization

The ability of beta-hemolytic group A streptococci, especially in the stationary phase, to invade respiratory epithelial cells was recently demonstrated (47, 94). Beta-hemolytic group A streptococci are mainly extracellular bacteria, but by specifically binding fibronectin, a protein that exists in human blood plasma and in the extracellular matrix, beta-hemolytic group A streptococci may be efficiently internalized into human mucosal cells. The fibronectin bound to the bacterial surface thereby acts like a bridging molecule with host cell integrins, which in turn initiate the uptake process that leads to internalization (45).

Sela & Barzilai (76) found that beta-hemolytic group A streptococcal strains were able to survive for 4–7 days inside cultured epithelial cells. They also found that beta-hemolytic group A streptococcal strains from patients with treatment failure harboured an internalization-associated gene in higher prevalence than strains recovered from patients in whom the streptococcal strains had been successfully eradicated. It is not known if internalization into host cells can influence the severity of beta-hemolytic group A streptococcal infections. Strains of streptococci show varying capacity to internalize (47, 94), and internalized beta-hemolytic group A streptococci have been found in asymptomatic carriers as well as in patients with pharyngotonsillitis (95**).** Strains from patients with treatment failure exhibit a significantly increased ability to survive intracellularly in cultured epithelial cells compared with strains from successfully treated patients (53). On the other hand, a beta-hemolytic group A streptococcal strain that was able to internalize in an animal model was less able to cause serious disease than beta-hemolytic group A streptococci without the internalizing capacity (59).

Disease manifestations

Beta-hemolytic group A streptococci are strict human pathogens giving rise to a wide range of infectious diseases. Impetigo, pharyngotonsillitis and erysipelas may be comparatively mild and are effectively treated with antibiotics. However, since the late 1980s, a rising number of life-threatening invasive beta-hemolytic group A streptococcal infections have been encountered, such as necrotizing fasciitis and streptococcal toxic shock syndrome (12, 36). Streptococci in these diseases are often restricted to certain M-types, in particular M1, and produce powerful superantigens, such as the pyrogenic exotoxin A, SpeA. Surgical intervention is often needed in the case of necrotizing fasciitis. However, in spite of antibiotics and intensive care, the mortality is high for patients with necrotizing fasciitis or streptococcal toxic shock syndrome (14, 19). Acute rheumatic fever, the most serious nonsuppurative complication of beta-hemolytic group A streptococcal

pharyngotonsillitis, is the leading cause of acquired heart disease among children in developing countries (5). Although no longer a significant health problem in most socioeconomically advanced countries, limited outbreaks of acute rheumatic fever occurred in the USA in the 1980s (88).

Acute poststreptococcal glomerulonephritis, a major cause of child renal failure, occurs after throat and skin infections with beta-hemolytic group A streptococci (87). Large epidemics are still occurring in developing countries, compared with sporadic cases in the developed world.

Clinical diagnosis

Signs and symptoms of acute pharyngotonsillitis include fever, throat angina, redness of the tonsils and pharynx, tonsillar exudate, enlarged and tender cervical lymph nodes, dysphagia and headache. Concurrent symptoms from the respiratory tract (e.g. cough or rhinorrhea) indicate a viral origin of the disease. Established beta-hemolytic group A streptococcal throat and skin infections in close surroundings of the patient such as at home, or in school or daycare centres, increases the probability of a beta-hemolytic group A streptococcal origin of the infection. Certain symptoms are more pronounced in pharyngotonsillitis of a beta-hemolytic group A streptococcal origin than in pharyngotonsillitis of another etiology. Thus, a high degree of redness in the throat (71), fever (30) and a shorter duration of symptoms before seeking medical care (79) correlate significantly with a beta-hemolytic group A streptococci etiology. The so-called Centor criteria have been widely used to implicate beta-hemolytic group A streptococci in adult patients and these are as follows: tonsillar exudates, tender anterior cervical adenopathy, fever by history and absence of cough. If three of these criteria are met, the positive predictive value for a beta-hemolytic group A streptococcal infection is 40–60% (11). The findings are, however, inconsistent and although the clinical picture may be of some guidance, it is seldom sufficient for establishing a reliable etiological diagnosis.

Microbiological diagnosis of beta-hemolytic group A streptococcal pharyngotonsillitis

As there are no pathognomonic signs or symptoms that can provide a definite diagnosis of beta-hemolytic group A streptococcal pharyngotonsillitis, the diagnosis depends on the identification of the bacterium. Bacterial identification can be performed by obtaining a throat culture or by a rapid antigen detection test. A good view of the pharynx and obtaining proper sampling technique are essential to achieve a representative sample. The specimen should be obtained from the tonsillar surface because beta-hemolytic group A streptococci in pharyngotonsillitis are predominantly localized on the tonsils and on the posterior oropharyngeal wall (48). The rapid antigen test requires more bacteria than required for culture. The quantity of sample material thus influences the sensitivity and specificity of the rapid tests, which are currently reported as being 74–97% and 89–95%, respectively (49, 58).

An asymptomatic carriage stage of beta-hemolytic group A streptococci is reported to occur in about 10% of adults and 25% of children during the winter season, although the estimates vary considerably (71). During large outbreaks of beta-hemolytic group A streptococcal pharyngotonsillitis, the carrier rate can be as high as 60% (21). A 4-year longitudinal study of 5–15-year-old schoolchildren found that the period during which a child carried beta-hemolytic group A streptococci of the same *emm* type averaged 10.8 weeks (range: 3–34 weeks). Many children, however, experienced several periods of carriage during the study and frequently exhibited switches in *emm* type (54). The risk of becoming a carrier of beta-hemolytic group A streptococci, as well as of contracting pharyngotonsillitis, is related to the period of time spent in close contact with a patient during the week preceding the onset of illness (18, 89). The reason why some individuals become carriers is unknown, but the carrier state appears to be a relatively harmless condition because it probably does not result in a clinical infection (39) and the streptococci are present in low numbers (71), which probably does not support a person-to-person transmission of the organism (21). However, problems arise if a carrier of beta-hemolytic group A streptococci acquires viral pharyngitis, because a positive test for beta-hemolytic group A streptococci raises the issue of antibiotic treatment. This example highlights the importance of a careful evaluation of symptoms in order to avoid unnecessary antibiotic treatment.

Laboratory findings

A correlation with leukocytosis (33, 71) or an increased level of C-reactive protein and beta-hemolytic group A streptococcal pharyngotonsillitis has been reported (40), whereas other investigators have

failed to verify such relationships (61, 70). Serological tests of anti-streptolysin O and anti-DNase B are of no diagnostic value in acute pharyngotonsillitis, but may be useful in the investigation of complications of the disease, such as rheumatic fever (69).

Reasons to treat beta-hemolytic group A streptococcal pharyngotonsillits

Beta-hemolytic group A streptococcal pharyngotonsillitis is a self-limiting disease and the routine use of penicillin V has therefore been questioned (25). However, beta-hemolytic group A streptococci are amongst the most virulent human pathogens, and patients with pharyngotonsillitis caused by infection with this bacterium can be seriously affected with high fever, dysphagia and severe pain. Although a majority of patients become free of symptoms within a week, irrespective of therapy, antibiotic treatment of pharyngotonsillitis caused by beta-hemolytic group A streptococci can significantly shorten the duration of symptoms (13, 16). Antibiotic treatment may also, to some extent, reduce the risk of purulent complications, such as peritonsillitis, otitis and sinusitis (13, 15, 93). In acute rheumatic fever, it is claimed that a majority of the patients have a history of pharyngotonsillitis. The decline of acute rheumatic fever in the developed world may indeed be the result of routine antibiotic use for beta-hemolytic group A streptococcal pharyngotonsillitis, supporting the present principles of treatment. Rheumatic fever is still a major health problem in many developing countries, and beta-hemolytic group A streptococci have been estimated to be the eighth most common source of global mortality caused by a single pathogen (10). In necrotizing fasciitis and streptococcal toxic shock syndrome, however, the port of entry of beta-hemolytic group A streptococci is seldom reported to be pharyngotonsillitis (14, 19).

In sum, the reasons for antibiotic treatment of beta-hemolytic group A streptococcal pharyngotonsillitis are: (i) more rapid alleviation of symptoms; (ii) reducing the spread of beta-hemolytic group A streptococci; and (iii) reducing the risk of suppurative and nonsuppurative complications. It is generally agreed that the benefits of antibiotic treatment outweigh the disadvantages (15, 34, 72).

Treatment of beta-hemolytic group A streptococcal pharyngotonsillitis

Penicillin V perorally for 10 days (12.5 mg / kg, two to four times daily) is currently the antibiotic therapy of choice for beta-hemolytic group A streptococcal pharyngotonsillitis. Despite over 50 years of use of penicillin, no penicillin-resistant beta-hemolytic group A streptococcal strains have so far been encountered. A possible explanation for this is that penicillin resistance in this species is not compatible with a virulent phenotype (29). In penicillin V treatment of beta-hemolytic group A streptococcal pharyngotonsillitis, a treatment period of at least 10 days should be imposed in order to achieve an acceptably low recurrence rate (27, 75, 82, 93). Despite the absence of penicillin resistance, treatment failure of beta-hemolytic group A streptococcal pharyngotonsillitis is as high as 5–25% (82). A second course of penicillin V treatment is followed by still higher failure rates (41), in some cases necessitating tonsillectomy.

Cephalosporins have been shown to be more effective than penicillin V in treating primary beta-hemolytic group A streptococcal pharyngotonsillitis (37, 55, 67). Cephalosporins may enable shorter treatment regimens than penicillin V, and some patients may only need to be dosed once daily (68). Cephalosporins are less susceptible to the β-lactamases produced by oral bacteria and probably exert a lesser impact on bacteriocin-producing alpha-hemolytic streptococci in the throat (37, 73).

Treatment of recurrent beta-hemolytic group A streptococcal pharyngotonsillitis with clindamycin instead of penicillin V seems to produce a significantly better clinical outcome (6, 62). This may be a result of the intracellular accumulation and a high concentration of clindamycin in tonsillar surface fluid (61).

Penicillin V, as a result of its narrow antimicrobial spectrum and the absence of penicillin resistance among beta-hemolytic group A streptococci, is still regarded as the drug of choice for primary beta-hemolytic group A streptococcal pharyngotonsillitis. Cephalosporins or clindamycin appear to be appropriate alternatives for patients experiencing recurrence of pharyngotonsillitis after penicillin V treatment.

The problem of frequent recurrence of beta-hemolytic group A streptococcal pharyngotonsillitis in patients is sometimes resolved by performing tonsillectomy, although opinions differ as to the benefit and risks of this treatment (8, 65, 66). In a Cochrane Review from 2000, no studies fulfilled the inclusion criteria for evaluating the effectiveness of tonsillectomy in adults with chronic / recurrent acute pharyngotonsillitis. Only two studies fulfilled the

criteria assessing the benefit of tonsillectomy in children with chronic/recurrent acute pharyngotonsillitis, and only limited conclusions could be drawn from these studies (8). Further studies are needed to evaluate the effectiveness of tonsillectomy in relation to pharyngotonsillitis.

Reasons for recurrence of beta-hemolytic group A streptococcal pharyngotonsillitis after penicillin V treatment

Possible factors that may lead to recurrence after penicillin V treatment of pharyngotonsillitis include low patient compliance, re-infection from the environment, eradication of alfa-hemolytic streptococci with inhibitory effects on beta-hemolytic group A streptococci, an increase in beta-lactamase-producing bacteria inactivating the drug, penicillin-tolerant streptococci, a low antibiotic concentration at the site of infection and intracellular beta-hemolytic group A streptococci surviving therapy (Table 2).

Low compliance

Treatment of beta-hemolytic group A streptococcal pharyngotonsillitis with penicillin V results in rapid recovery (16, 93). As the patient is often free of symptoms after 2–3 days of treatment, they may consider further medication as unnecessary and prematurely discontinue the antibiotic treatment, raising the odds of treatment failure.

Re-infection from the environment

As family members and other close contacts of patients with beta-hemolytic group A streptococcus pharyngotonsillitis are often infected with the same strain, recurrence may be caused by re-infection from other individuals (22).

Table 2. Possible causes of recurrence of beta-hemolytic group A streptococcal pharyngotonsillitis after treatment with penicillin V

Low compliance
Re-infection from the environment
Eradication of alfa-hemolytic streptococci by penicillin V
Increase in beta-lactamase-producing bacteria capable of inactivating penicillin V
Penicillin-tolerant beta-hemolytic group A streptococci
Low antibiotic concentration at the site of infection
Intracellular beta-hemolytic group A streptococci capable of surviving therapy with penicillin V

Alpha-hemolytic streptococci with inhibitory effect on beta-hemolytic group A streptococci

Some alpha-hemolytic streptococci produce bacteriocins with inhibitory activity against beta-hemolytic group A streptococci. Eradication of alpha-hemolytic streptococci by penicillin V will theoretically reduce bacterial interference and thus increase the risk of treatment failure (74). However, some investigations have failed to show that lack of bacterial interference was related to bacterial treatment failure in beta-hemolytic group A streptococcal pharyngotonsillitis (27). On the other hand, administration of alpha-hemolytic streptococci into the throat following β-lactam treatment of beta-hemolytic group A streptococcal pharyngotonsillitis has been able to reduce the recurrence rate (23, 73). However, replacement treatment with alpha-hemolytic streptococci is not yet commercially available.

Increase in β-lactamase-producing bacteria inactivating the drug

Treatment with penicillin V will promote selection of bacterial species producing β-lactamase, conceivably accounting for the inactivation of penicillin V (7, 84). However, studies on penicillin V vs. amoxicillin/clavulanic acid in the treatment of pharyngotonsillitis have been inconclusive (41, 83). Gerber et al. (27) studied penicillin V and cefadroxil in the treatment of primary beta-hemolytic group A streptococcus pharyngotonsillitis and found no evidence that β-lactamases produced by the normal pharyngeal flora were related to bacterial treatment failure. The role of β-lactamases in treatment failure thus remains unclear.

Penicillin tolerance

Tolerance to β-lactam antibiotics is a known phenomenon in some medically important species, such as *Enterococcus faecalis*, *Streptococcus pneumoniae* and various alpha-hemolytic streptococci (85), and appears to account for the failure of penicillin therapy of *Arcanobacterium haemolyticum* infections (60). Penicillin tolerance of beta-hemolytic group A streptococci has been suggested to account for the failure in penicillin V treatment of beta-hemolytic group A streptococcal pharyngotonsillitis, but reports have been contradictory, conceivably because of the variability in the definition of 'tolerance' as well as the technical pitfalls of the methods used (42, 44, 63, 78, 80). The existence of penicillin tolerance in

beta-hemolytic group A streptococci has also been questioned (91).

Low antibiotic concentration at the site of infection

The beta-hemolytic group A streptococci causing acute pharyngotonsillitis are mainly present in the secretion on the tonsillar surface and in the crypts rather than in the parenchyma (17, 48). Penicillin V was detected in tonsillar surface fluid in a majority of patients on the first day of treatment of acute beta-hemolytic group A streptococcus pharyngotonsillitis, but despite a high concentration in serum, was rarely present on the 10th day or in healthy, treated subjects (81). Insufficient concentrations of antibiotics in tonsillar surface fluid may contribute to treatment failure of beta-hemolytic group A streptococcal pharyngotonsillitis (64).

Intracellular beta-hemolytic group A streptococcal surviving therapy

Beta-hemolytic group A streptococci may reside in epithelial cells of pharyngotonsillitis lesions, and may not be reached by penicillin V. Österlund et al. (95) found that beta-hemolytic group A streptococci, which were internalized in human respiratory epithelial cells and grown in an antibiotic supplemented medium, were externalized as soon as the extracellular antibiotic was removed and an extracellular infection developed rapidly thereafter. Thus, respiratory epithelial cells may act as a reservoir for internalized beta-hemolytic group A streptococci and have the potential to cause infection after termination of a penicillin V treatment. The extent to which epithelial cell-embedded beta-hemolytic group A streptococci cause recurrence of pharyngotonsillitis after penicillin V treatment remains to be determined.

Bacteria other than beta-hemolytic Group A streptococci

Nongroup A beta-hemolytic streptococci

Group C and group G streptococci may cause pharyngotonsillitis, especially in older children and adults (35). Rapid tests for detecting these streptococcal groups are not available and thus bacterial culture is needed for diagnosis. Evidence suggests that group C and group G streptococci can cause acute poststreptococcal glomerulonephritis, but not rheumatic fever.

Arcanobacterium hemolyticum

A. hemolyticum is an uncommon cause of pharyngotonsillitis and is often associated with a rash that may mimic scarlatina (1). The disease is found most commonly in individuals of the 15–18 years age-group and the incidence is about 2.5% among patients with pharyngotonsillitis in this age group (52). The organism must be cultured on specific media and is not sensitive to penicillin but is sensitive to macrolides. *A. hemolyticum*-related pharyngotonsillitis is self-limiting with no known complications.

Corynebacterium diphtheriae

Pharyngotonsillitis caused by to *C. diphtheriae* was relatively common during World War II, but has rapidly declined in Europe since that time. In a vaccinated population the disease is very rare. However, *C. diphtheriae*-related pharyngotonsillitis is not uncommon in the former Soviet Union countries where its incidence is probably under-reported.

The pharyngotonsillitis caused by *C. diphtheriae* is characterized by grey membranes in the throat, larynx and around the nostrils. Bleeding occurs if attempts are made to remove the membranes. The bacteria produce an exotoxin that gives rise to myocarditis and neurological complications with paralysis and polyneuropathia. Treatment with parenteral antibiotics and specific immunoglobulin should be started immediately and even before the microbiological diagnosis in cases of a high suspicion of *C. diphtheriae*-related pharyngotonsillitis.

Vincent's angina

Vincent's angina is an uncommon infection presenting with unilateral necrotizing tonsillitis, caused by a mixed anerobic and aerobic flora of spirochetes, bacteroides, streptococci and fusiform bacteria. Penicillin is the drug of choice. The patient must be followed-up after a couple of weeks to rule out malignancy, because carcinoma of the tonsils can show a similar clinical picture.

Neisseria gonorrhoeae

N. gonorrhoeae may be a cause of pharyngotonsillitis in individuals practising oral sex. A study of patients with sore throats in a general medical practice found the prevalence of *N. gonorrhoeae* to be about 2% (43). About 10% of patients with genital gonorrhoea have

throat cultures positive for *N. gonorrhoeae* and are often asymptomatic. *N. gonorrhoeae* must be grown on specific media. Antibiotic treatment is needed to prevent transmission as well as further dissemination of the organism and the disease.

Mycoplasma pneumoniae, Chlamydia pneumoniae

Pharyngotonsillitis involving *M. pneumoniae* or *C. pneumoniae* is frequently accompanied by bronchitis. Infections with these two bacteria often affect children and young adults.

Nonbacterial pharyngotonsillitis

Epstein–Barr virus / mononucleosis

Most individuals become infected with Epstein–Barr virus during childhood and will only experience a subclinical infection or mild pharyngitis. However, about one-third of individuals who become infected during adolescence develop the mononucleosis syndrome. Infectious mononucleosis is a systemic disease characterized by pharyngotonsillitis, nodular fever and septicemia. Patients show prominent exudate and swelling of the tonsils, cervical adenopathy, hepatomegaly and often splenomegaly. Mononucleosis patients with beta-hemolytic group A streptococcal pharyngotonsillitis show a prolonged course of pharyngotonsillitis, fever, fatigue and tender cervical adenopathy. Heterophile antibodies are not detectable until several weeks after the onset of mononucleosis, but immunoglobulin M specific antibodies against capsid and early Epstein–Barr virus antigens can be helpful for early diagnosis. Mononucleosis in most patients will resolve without special treatment. Some patients having difficulty with swallowing and breathing will need hospital care. Cytomegalovirus causes about 10% of mononucleosis cases, and hepatitis is more evident than with Epstein–Barr virus-related disease. Testing for specific cytomegalovirus antibodies are of diagnostic importance.

Primary human immunodeficiency virus infection

The clinical presentation of a primary human immunodeficiency virus (HIV) infection may mimic that of Epstein–Barr virus mononucleosis. The incubation period is about 2–3 weeks. The acute HIV syndrome presents with pharyngotonsillitis, weight loss, fever, adenopathy, rash and splenomegaly. Laboratory tests often show lymphopenia and increased transaminase levels (38). Tests for anti-HIV immunoglobulins are often negative in the early disease stages but detection of HIV RNA by polymerase chain reaction is helpful in providing a diagnosis. It is important to establish the HIV diagnosis as early as possible to initiate an appropriate antiviral therapy.

Influenza virus

Pharyngotonsillitis caused by influenza virus is often exudative. The disease usually occurs in major outbreaks and is often associated with myalgias, fever, tracheitis and headache. Rapid tests for the detection of influenza A and B viruses may be useful, and antiviral therapy may reduce the illness duration by about 24 h but is seldom advocated.

Adenovirus

Adenovirus is a common cause of pharyngotonsillitis. Pharyngotonsillitis caused by adenovirus often presents as pharyngoconjunctival fever (57). The disease is otherwise difficult to distinguish from pharyngotonsillitis caused by other pathogens.

Herpes simplex virus

Pharyngotonsillitis caused by herpes simplex virus often appears with vesicles and ulcerative lesions of the mouth and gingiva, and the disease occurs most frequently in children. The throat pain can be very severe, and hospitalization and parenteral nutrition may be indicated. Herpes simplex virus type 1 is by far the most common cause of the disease, but herpes simplex virus type 2 can present similar clinical manifestations.

Coxsackie A virus / herpangina

This coxsackie A enterovirus can give rise to pharyngotonsillitis that is characterized by small vesicles surrounded by a red halo in the posterior palate. The disease is virtually always seen in children.

Noninfectious pharyngotonsillitis

Agranulocytosis and leukaemia might occasionally start as a severe pharyngotonsillitis that does not

respond to antibiotics. Laboratory blood tests are needed to confirm the diagnosis.

Periodic fever syndrome characterized by repeated episodes of pharyngotonsillitis with cervical adenopathy, fever, headache, nausea, reduced general condition and elevated C-reactive protein can occur in children with no proven etiological pathogen. There is no evidence-based treatment, but tonsillectomy is considered to have an effect (96).

Summary

Acute pharyngotonsillitis is a common illness with the highest incidence occurring during the winter season. Viruses account for more than half of the cases of pharyngotonsillitis. Beta-hemolytic group A streptococci are the etiological agents in 15–30% of cases, with higher figures observed during the winter months. Beta-hemolytic group A streptococci are virulent human pathogens, which may cause suppurative and nonsuppurative complications, and sometimes life-threatening diseases such as necrotizing fasciitis and streptococcal toxic shock syndrome. Signs and symptoms of a beta-hemolytic group A streptococcal infection include tonsillar exudate, tender anterior cervical adenopathy, a history of fever and absence of a cough, but the findings are rather inconsistent. Identification of the bacterium by culture or by a rapid antigen test is needed to establish a definite diagnosis. Penicillin V for 10 days is the drug of choice in primary beta-hemolytic group A streptococcal pharyngotonsillitis. Although penicillin resistance is not recorded in beta-hemolytic group A streptococci, penicillin V treatment fails in as many as 5–25% of the patients, and higher failure rates can occur after a second course of penicillin V treatment, sometimes necessitating tonsillectomy. Factors potentially contributing to antibiotic treatment failure include low compliance rate, reinfection from the environment, eradication of alfa-hemolytic streptococci with an inhibitory effect on beta-hemolytic group A streptococci, an increase in beta-lactamase-producing bacteria inactivating the drug, penicillin-tolerant streptococci, low antibiotic concentration at the site of infection, and intracellular beta-hemolytic group A streptococci surviving therapy. Treatment with cephalosporins or clindamycin has been reported to result in a less frequent recurrence of beta-hemolytic group A streptococcal pharyngotonsillitis and is advocated in patients with beta-hemolytic group A streptococcus pharyngotonsillitis not responding to penicillin V treatment.

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